Remarks

Amendments to the Claims

Claim 57 is amended to correct a clerical error, *i.e.*, to replace an inadvertent second occurrence of "(c)" with "(d)."

Claims 59 and 60 are amended to be in independent form by incorporating the subject matter of independent claim 28. The amendments add no new matter, do not require a new search, do not require consideration of any new issue, and specifically comply with a requirement of form expressly set forth in the Final Office Action.

Objection to Claims 59 and 60

Claims 59 and 60 are objected to because they depend from rejected claim 28. Claims 59 and 60 have been amended to incorporate the subject matter of claim 28. Please withdraw the objection.

Rejection of Claims 32 and 56-58 Under 35 U.S.C. § 112 ¶ 1

Claims 32 and 56-58 stand rejected under 35 U.S.C. § 112 ¶ 1 as insufficiently described. Applicants respectfully traverse the rejection.

The first paragraph of 35 U.S.C. § 112 requires the specification to provide a written description of the claimed invention:

> [t]he specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

In a written description inquiry, "[t]he primary consideration is *factual* and depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure." In the factual inquiry, the teachings of the specification must be considered as a whole. *In re Wright*, 866 F.2d 422, 425, 9 U.S.P.Q.2d 1649, 1651 (Fed. Cir. 1989).

The specification must be considered from the viewpoint of a skilled artisan at the April 28, 1996 priority date of this application. *Wertheim*, 541 F. 2d at 262, 191 U.S.P.Q. at 96. A specification adequately describes a genus to the skilled artisan if it permits the artisan to "visualize or recognize members of the genus." *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1568, 43 U.S.P.Q.2d 1398, 1406 (Fed. Cir. 1997).

The recited molecular complex contains two ligand binding sites. Dependent claims 32 and 56-58 recite that an identical antigenic peptide is bound to each ligand binding site recited in independent claim 28. The Final Office Action asserts that the written description requirement for the genus of antigenic peptides can be satisfied only by a disclosure of specific molecules. Final Office Action mailed April 20, 2006 at pages 2 and 3. The rejection is legally incorrect.

First, the specification preferably does not describe what is known in the art. *Hybritech v. Monoclonal Antibodies*, 802 F.2d 1367, 1384, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986). *See also* M.P.E.P. § 2163(II)(A)(3)(a) ("[t]he description need only describe in detail that which is new or not conventional in the art.") and the Revised Interim Written Description Guidelines Training Materials at page 4. In contrast to the molecular complex itself, "antigenic peptides" are neither new nor unconventional in the art. They do not require explicit description to be understood by those skilled in the art. See pages 2-4 of Applicants' response filed March 8, 2005.

The Final Office Action cites several cases, but none applies to the rejected claims. The Examiner draws an analogy between the genus of antigenic peptides recited in claims 32 and 56-58 and the genus of nucleic acids claimed in *Regents of the University of California v. Lilly*. Final Office Action at page 3, lines 4-7. The Examiner cites *University of Rochester v. G.D. Searle Co.*, 69 U.S.P.Q.2d 1886, 1892 (Fed. Cir. 2004) for the proposition that "generalized language may not suffice if it does not convey the detailed identity of an invention." Final Office Action at page 3 (quoting *University of Rochester*, 69 U.S.P.Q.2d at 1892). The Examiner cites *Noelle v. Lederman*, 69 U.S.P.Q.2d 1508, 1545 (Fed. Cir. 2004) for the proposition that "a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. Final Office Action at page 4. None of the cited caselaw is apt. Dependent claims 32 and 56-58 merely add a recitation of a well-known class of molecules – antigenic peptides – which are bound to ligand binding sites of the recited molecular complex.

The rejection under 35 U.S.C. § 112 ¶ 1 has no legal foundation. The specification adequately describes the invention of dependent claims 32 and 56-58 because it describes the "new and unconventional" subject matter encompassed within those claims. Applicants respectfully request withdrawal of the rejection.

Rejection of Claims 28-31 and 51-55 Under 35 U.S.C. § 103(a)

Claims 28-31 and 51-55 stand rejected under 35 U.S.C. § 103(a) as obvious. Applicants respectfully traverse the rejection.

Section 103(a) of 35 U.S.C. states:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

Obviousness under 35 U.S.C. § 103(a) is a question of law based on several factual inquiries:

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved.

Graham v. John Deere Co., 383 U.S. 1, 17 (1966). A *prima facie* case of obviousness must be based on specific factual findings resulting from the *Graham* inquiries:

> [D]eficiencies of the cited references cannot be remedied by the Board's general conclusions about what is "basic knowledge" or "common sense" to one of ordinary skill in the art. . . . This assessment of basic knowledge and common sense was not based on any evidence in the record and, therefore, lacks substantial evidence support. . . . With respect to core factual findings in a determination of patentability, however, the Board cannot simply reach conclusions based on its own understanding or experience -- or on its assessment of what would be basic knowledge or common sense. Rather, the Board must point to some concrete evidence in the record in support of these findings.

In re Zurko, 59 U.S.P.Q.2d 1693, 1697 (Fed. Cir. 2001). *See also In re Kotzab*, 55 U.S.P.Q.2d 1313, 1317 (Fed. Cir. 2000) ("Whether the Board relies on an express or an implicit showing [of motivation], it must provide particular findings related thereto . . . . Broad conclusory statements

standing alone are not 'evidence.'"); *In re Lee*, 277 F.3d 1338, 1343-44, 61 U.S.P.Q.2d 1430, 1434 (Fed. Cir. 2002) ("This factual question of motivation is material to patentability, and could not be resolved on subjective belief and unknown authority. . . . [T]he Board rejected the need for 'any specific hint or suggestion in a particular reference' to support the combination of the Nortrup and Thunderchopper references. Omission of a relevant factor required by precedent is both legal error and arbitrary agency action.").

The burden of establishing that a claimed invention is *prima facie* obvious rests with the Examiner. The *prima facie* case requires a showing that the cited prior art teaches or suggests all the claim limitations. *In re Royka*, 490 F.2d 981, 985, 180 U.S.P.Q. 580, 583 (C.C.P.A. 1974); *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970). The *prima facie* case also requires a showing that one of ordinary skill would have been motivated to combine the cited references. *In re Linter*, 458 F.2d 1013, 1016, 173 U.S.P.Q. 560, 562 (C.C.P.A. 1972). Finally, the *prima facie* case requires a showing that one of ordinary skill in the art would have had a reasonable expectation that the asserted combination or modification would be successful. *In re Merck & Co.*, 800 F.2d 1091, 1097, 231 U.S.P.Q. 375, 379-80 (Fed. Cir. 1986).

The cited references must be considered in their entireties, including portions that would have led the ordinary artisan away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1550, 220 U.S.P.Q. 303, 310 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). Hindsight use of an applicant's specification is improper. *In re Kotzab*, 217 F.3d 1365, 1371, 55 U.S.P.Q.2d 1313, 1317 (Fed. Cir. 2000).

The rejection

The rejection is based on a combination of four references: Matsui[1] (the primary reference), Dal Porto,[2] Chang,[3] and Harris.[4] The rejection cites Matsui as teaching that "the interaction between monovalent TCRs and MHC heterodimers has been difficult to study directly due to the very low affinity between these molecules." Office Action mailed August 11, 2005 at page 5, ¶ a. The rejection cites Chang as teaching that "the fusion of peptide sequences known to form unique, heterodimeric coiled-coils to the C-termini of the TCR α and β extracellular segments promotes heterodimer formation over homodimer formation. *Id.* at page 6 ¶ c. The rejection cites Harris as demonstrating "that binding domains (including cell surface receptors) can be fused via a linker to the N-terminus of heavy and light chain variable regions without altering the binding function of the fusion proteins." *Id.* at page 6 ¶ d. The rejection cites Dal Porto as disclosing high affinity divalent class I MHC/IgG molecules which have nanomolar affinity for T cell receptors and which, in contrast to monovalent MHC class I molecules, inhibit lysis of target cells. *Id.* at pages 5-6 ¶ b.

The gist of the rejection is that the recited molecular complex would have been obvious because high affinity, divalent soluble TCR and class II molecules are desirable (Matsui), MHC class I/Ig molecules have higher affinity for TCRs than do monovalent MHC class I molecules (Dal Porto), heterodimer formation can be facilitated using leucine zippers (Chang), and binding

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[1] Matsui *et al.*, *Proc. Natl. Acad. Sci. U.S.A. 91*, 12862-66, December 1994.

[2] Dal Porto *et al.*, *Proc. Natl. Acad. Sci. U.S.A. 90*, 6671-75, 1993.

[3] Chang *et al.*, *Proc. Natl. Acad. Sci. USA 91*, 11408-412, 1994.

[4] Harris *et al.*, WO 94/09131, April 28, 1994.

domains which are fused to the N termini of heavy and light chains retain their binding function (Harris).

The Examiner did not evaluate the cited references under the proper legal standards

The Examiner did not evaluate the cited references under the proper legal standards. The rejection set forth above ignores large portions of each reference, including a portion of Chang that explicitly teaches away from the invention. Instead, using the specification as a template, the Examiner selected isolated teachings of the cited references and modified and combined them without regard to what each of the references teaches as a whole. This is clear legal error. *Gore*, 721 F.2d at 1550, 220 U.S.P.Q. at 310; *Kotzab*, 217 F.3d at 1371, 55 U.S.P.Q.2d at 1317.

The remainder of this response analyzes the cited references under the proper legal standards for determining obviousness. The analysis demonstrates that the cited references – even if, *arguendo*, properly combined – do not render claims 28-31 and 51-55 *prima facie* obvious.

Scope and content of the prior art

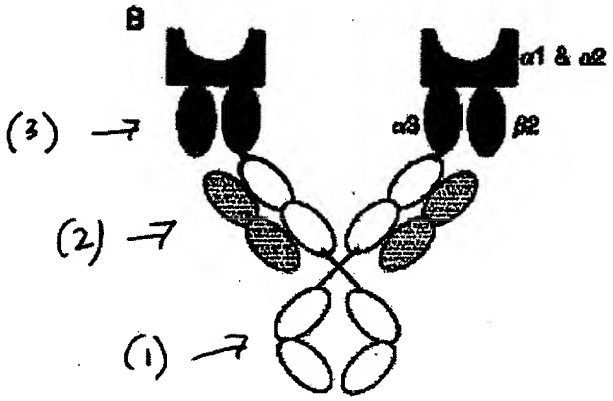
Matsui. The primary reference, Matsui, addresses the problem of how to obtain direct measurements of the binding kinetics between a soluble TCR and a peptide presented by a soluble MHC molecule. Matsui acknowledges that soluble TCRs are available and that several studies have determined that the binding affinities between soluble TCRs and peptides presented by soluble MHC molecules are relatively low (K_d of 4-6 x 10^{-5} M, 10^{-4}-10^{-7} M, and 10^{-5} M, respectively). Matsui points out that these measurements were indirect, however, which is a disadvantage:

> However, none of these studies give direct information about the kinetics of the molecular interactions and are dependent on live

> cells, thus greatly limiting the range of conditions (temperature, ionic strength, etc.) that can be assessed.

Matsui at page 12862. Matsui teaches use of surface plasmon resonance to overcome the disadvantages of indirect measurements so that low affinity interactions between a soluble TCR and a peptide presented by a soluble MHC molecule can be studied directly.

Dal Porto. Dal Porto teaches a class I MHC/IgG complex which comprises an immunoglobulin molecule and two MHC class I molecules[5] (Figure 1B):



The Dal Porto complex comprises two of a single species of fusion protein **(1)**: an immunoglobulin heavy chain (white) fused to the α_3 subunit of the α chain of a class I MHC molecule (black). Neither the immunoglobulin light chains **(2)** nor the β_2 microglobulin subunits **(3)** are part of a fusion protein. The β_2 microglobulin subunit associates with the MHC class I α chain as it normally does in a native class I MHC molecule. The immunoglobulin light chain associates with the immunoglobulin heavy chain as it does in a native immunoglobulin molecule.

Chang. Chang teaches a method of making a soluble TCR. Chang fused segments of 30 amino acids to the carboxyl termini of TCR α and β extracellular domains via a flexible linker.

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[5] As indicated in Figure 1B, a class I MHC molecule comprises an α chain of three segments (α1, α2, and α3) and a β_2 microglobulin subunit.

The fused segments associate to form a leucine zipper, which faciliates pairing of the TCR α and β subunits. Page 11408, col. 2.

Chang teaches that use of leucine zipper components "should be broadly useful in the efficient production and purification of TCRs as well as other heterodimeric proteins." Abstract. See also page 11412, paragraph bridging columns 1 and 2:

> **Implications.** A protein engineering methodology using recombinant DNA techniques to greatly increase the efficiency in heterodimer formation between TCR α and β subunits has been developed. This approach involves appending related but distinct peptide sequences (BASE-p1 and ACID-p1) to the carboxyl termini of the α and β subunits, respectively. BASE-p1 and ACID-p1 peptides generate a stable coiled coil structure, thereby favoring subunit association. The interaction between these synthetic leucine zipper components is restricted due to their electrostatics such that, unlike with TCR-ζ fusion proteins, homodimers are not permitted. This approach makes it possible to bring together at will two distinct subunit components. In principle, it should now be possible to facilitate association of any type of naturally occurring heterodimeric structure including, for example, MHC class II α and β subunits or CD8α and CD8β components. Associations between individual protein domains such as TCR V_α and V_β can be fostered in the absence of other protein segments (C_α and C_β). In addition, it should also be possible to force association between proteins that may never or only transiently come in contact with one another, thereby offering a means to better understand regulatory events affecting cellular activation, cell cycle control, gene transcription, or cellular differentiation.

Paragraph bridging columns 1 and 2 of page 11412. There is no teaching in Chang to use anything <u>other</u> than leucine zipper components to associate heterodimeric proteins.

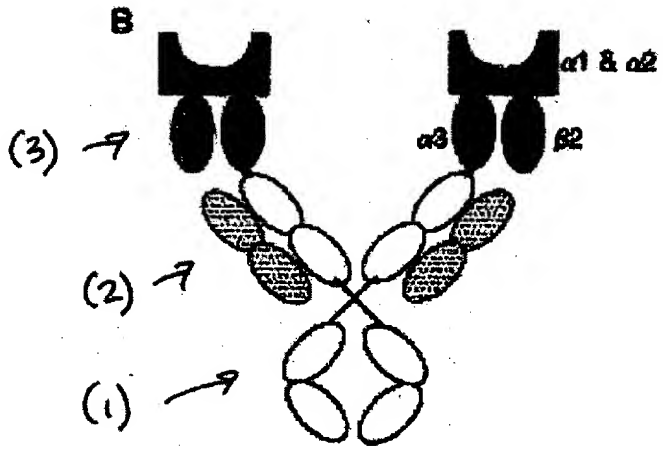
Harris. Harris teaches "recombinant bispecific (heterodimeric) and/or monodimeric bivalent specific binding proteins, for example antibodies, in which the specific association of the component modules is accomplished by using the recognition and natural homo- or hetero-dimerization of additionally fused associating domains." Page 8, lines 13-19. The bulk of the

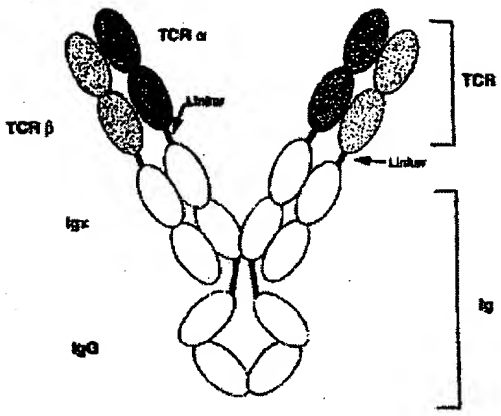
Harris disclosure relates to antibodies. The disclosed purpose of the binding proteins is to provide high affinity antibodies, particularly bispecific antibodies, which are not immunogenic in humans and which do not have the undesirable effector functions of complete antibody molcules: "the effector functions intrinsic to complete antibody molecules (such [as] Fc receptor and complement binding) have led to undesirable interactions." Harris, paragraph bridging pages 1 and 2.

> The cited combination of references does not teach or suggest all elements of the claimed subject matter, which differs substantially from the contents of the cited references.

The recited molecular complex differs significantly from what would be obtained even if, *arguendo*, the teachings of the cited references were combined as the Examiner asserts. That is, the cited combination of references does not teach or suggest all elements of the claimed invention. This ground alone is sufficient to defeat the alleged *prima facie* case of obviousness. See M.P.E.P. § 2142 ("the prior art reference (or references when combined) must teach or suggest all the claim limitations").

For example, the molecule of Dal Porto (left; Fig. 1B) and one embodiment of the recited molecular complex (right; specification Fig. 1D) are illustrated below:





Dal Porto, Fig. 1B

specification, Fig. 1D

As described above, Dal Porto's complexes comprise a single species of fusion protein which consists of the immunoglobulin heavy chain and the MHC class I α chain (consisting of α1, α2, and α3 segments) **(1)**. The β_2 microglobulin subunit **(3)** associates with the α chain as it normally does in a native class I MHC molecule. The immunoglobulin light chain **(2)** associates with the immunoglobulin heavy chain as it does in a native immunoglobulin molecule. Neither the immunoglobulin light chains nor the β_2 microglobulin subunits are part of a fusion protein. Thus, Dal Porto's complex contains only a single species of fusion protein.

In contrast, the recited molecular complexes comprise two types of fusion proteins. One fusion protein of the recited complex comprises an extracellular portion of a first transmembrane polypeptide (TCRα in Fig. 1D) and an immunoglobulin heavy chain **(4)**. The other species of fusion protein comprises an extracellular portion of a second transmembrane polypeptide (TCRβ in Fig. 1D) and an immunoglobulin light chain **(5)**. In Dal Porto's complex, neither the β2 microglobulin nor either of the light chains is part of a fusion protein.

Thus, contrary to the Examiner's assertion in the final Office Action, the recited molecular complexes do not "merely differ from the molecular complex of Dal Porto *et al.* by substitution of the extracellular domains (alpha and beta subunits) of the TCR and class II MHC molecules in place of the class I MHC portion of the molecule of Dal Porto *et al.*" Final Office Action at page 8 ¶ 1. Such a substitution – which Dal Porto neither teaches nor suggests – would not have formed the recited molecular complex, which requires two distinct types of fusion proteins. In fact, modifying Dal Porto's molecule to arrive at a molecular complex such as that in Figure 1D of the specification, for example, requires two significant modifications: (1) fusing the extracellular domain of a first transmembrane polypeptide to the immunoglobulin heavy chain in place of the class I MHC α chain (as the Examiner argues) and (2) fusing the extracellular domain of a second transmembrane polypeptide to the immunoglobulin's light chain. The prior art neither teaches nor suggests the latter modification.

> One of ordinary skill in the art would have had no motivation to select isolated elements of the cited references and modify and combine them as the Examiner asserts.

The relevant question is not whether Matsui – or any other teaching in the art – would have motivated the ordinary artisan to make a divalent soluble MHC or TCR molecule as the Examiner contends. The relevant question is whether Matsui, in view of Chang, Harris, and Dal Porto, would have motivated one of ordinary skill to make the molecular complex recited in claims 28-31 and 51-55. The answer is no.

Matsui simply teaches a method to obtain direct measurements of interactions between a soluble TCR and a peptide presented by a soluble MHC complex. Matsui solves the problem of measuring interactions between these low-affinity binding partners; thus, Matsui as a whole

would not have motivated one of ordinary skill to make soluble TCR or MHC molecules with higher binding affinities.

Chang teaches no other method of associating polypeptides other than by using leucine zipper components. Polypeptides associated via a leucine zipper as taught in Chang are stabilized by interdigitation of leucine residues on two protein alpha-helices. The fusion proteins of the recited molecular complex, however, are not held together with leucine zippers as taught in Chang. Chang's teaching of leucine zippers would not have motivated an ordinary artisan to use immunoglobulin chains, which have a very different secondary structure. Those skilled in the art know that all domains of immunoglobulin chains such as those recited in the claims contain two layers of β-pleated sheet which have three or four strands of antiparallel polypeptide chain and that immunoglobulin chains are held together with disulfide bonds.[6]

Harris explicitly teaches one of ordinary skill not to include constant regions of an immunoglobulin molecule in its binding proteins. In fact, use of an immunoglobulin molecule would render the Harris binding proteins unsatisfactory for one of their intended purposes (to avoid undesirable effector functions). There is, therefore, no suggestion in Harris to include both heavy and light immunoglobulin chains, which are present in molecular complexes of the invention. *In re Gordon*, 733 F.2d 900, 902, 221 U.S.P.Q. 1125, 1127 (Fed. Cir. 1984); M.P.E.P. § 2143.01(V) ("If the proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification.").

Furthermore, those of skill in the art at the April 28, 1996 priority date of this application knew that no particular manipulation was needed to cause the extracellular domains of MHC

[6] Abbas *et al.*, eds., Cellular and Molecular Immunology, 3d ed., pages 41-43 (provided with the responsed filed January 11, 2006).

class II molecules or TCRs to associate to form functional peptide binding sites. It was well known that the two extracellular domains of TCR molecules or of class II MHC molecules will associate to form a peptide binding site in the absence of their transmembrane domains. That is, the ordinary artisan knew that one extracellular domain need not be anchored in any particular orientation relative to the other extracellular domain in order for the two extracellular domains to associate and form a functional peptide binding site. See U.S. Patent 5,723,309 and U.S. Patent 5,583,031, discussed at pages 8-9 of the response filed January 11, 2006. Thus, even if, *arguendo*, one of ordinary skill had been motivated to modify Dal Porto's complex to make a divalent TCR/IgG or class II MHC/IgG molecule, the modification would have been to substitute one of the TCR or class II MHC extracellular domains for the MHC class I α chain in the fusion protein, to express the other extracellular domain by itself, and to permit the two extracellular domains to associate as the prior art taught they would.

But this modification would not have formed the present invention. To form the recited molecular complexes, the second extracellular domain must be fused to the immunoglobulin light chain. None of the cited prior art motivates, teaches, or suggests associating the extracellular domains of a TCR or MHC class II molecule by fusing the domains to an immunoglobulin heavy and light chain, respectively.

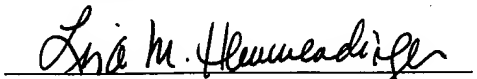
Properly considered in their entireties, the combination of Matsui, Chang, Harris, and Dal Porto do not make the recited molecular complexes *prima facie* obvious. Matsui does not suggest construction of any molecules with higher binding affinities. Harris teaches away from using immunoglobulin heavy and light chains, which the recited molecular complexes comprise. Chang teaches use of leucine zipper components to associate extracellular TCR domains, but the recited molecular complexes contain β pleated sheets, not a leucine zipper. Dal Porto teaches a

molecule with a substantially different structure. The rejection does not make any specific factual findings to support the notion that one of ordinary skill would have been motivated to combine the cited references, much less to make the extensive modifications necessary to make the present invention.

Respectfully submitted,

BANNER & WITCOFF, LTD.

Date: July 20, 2006

By: 

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